Specialty Conference

Hypertension Symposium: Newer Topics on Normal and Abnormal Blood Pressure Regulatory Mechanisms

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*F*or years essential hypertension was regarded as a relatively uniform disease having one predominant but uncertain cause. We now recognize that blood pressure is regulated by an interplay of factors that include vascular hemodynamics, pressor and depressor hormones, volume and sodium alterations, neural stimuli and renal dynamics. It is now clear that no single aberration can explain this disorder. Whether a person with essential hypertension has one or multiple pathophysiologic changes is still debated just as vigorously as the concept that patients who have this disorder can be neatly divided into subsets based on differences in certain blood pressure regulatory systems.

This conference focuses on several new and controversial areas in the pathogenesis of essential hypertension. Cellular sodium transport abnormalities have recently been rediscovered in this disorder and add new evidence to the concept that sodium may have an important role in essential hypertension. Other epidemiologic factors have taken on new importance in blood pressure control, and obesity and its attendant metabolic aberrations serve as an excellent example of this problem. The renin-angiotensin system is one of the best characterized blood pressure control systems in essential hypertension. Yet only recently with the ability to block the effect of angiotensin II has the participa-

tion of this system in essential hypertension been better defined. The recently discovered complexity of the components of this system (inactive renin, tissue renins) has introduced new thoughts on its role in blood pressure control. The ultimate goal in drug treatment of essential hypertension would be the use of agents that specifically attack a given abnormality. The introduction of the converting enzyme inhibitors and calcium channel blockers may be a step in this direction.

Sodium Transport in Hypertension

MICHAEL TUCK, MD:* A cause-effect relationship between sodium intake and hypertension was one of the earliest considerations in the pathogenesis of this disorder. Numerous epidemiologic studies show a strong correlation of average daily salt intake and the prevalence of hypertension in different geographic areas.[1] It has been more difficult, however, to establish this relationship in societies wherein salt intake is high and examination of blood pressure levels in normal persons with varying salt intakes may not show any differences. It is possible, however, that within populations the level of blood pressure of certain persons or families is more dependent on salt intake. This differing sus-

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ABBREVIATIONS USED IN TEXT

G6PD = glucose-6-phosphate dehydrogenase
K_m = Michaelis-Menten constant

ceptibility to high salt intake may have a genetic basis and may originate in the mechanisms whereby sodium is transported across cell membranes. The concept of salt susceptibility was first championed by Lewis K. Dahl,[2] who developed a strain of rats that responded to high salt intake by having pronounced hypertension develop and another strain in which blood pressure was resistant to high salt intake. Although not yet proved, these findings in experimental hypertension are possibly comparable to human essential hypertension. Another early observation from Tobian[3] was that cardiovascular tissues from patients who have hypertension have a higher sodium content than those from their normotensive counterparts. One explanation for high intracellular sodium in hypertension is that sodium transport pathways may be abnormal in the cells of hypertensive persons.

In 1960 Losse and co-workers first noted high intracellular sodium concentration in erythrocytes of essential hypertensive patients and suggested this was due to abnormal sodium transport in this cell.[4] Most cation transport studies in human hypertension have been on erythrocytes, polymorphonuclear leukocytes or lymphocytes because of their accessibility. In human erythrocytes the extrusion of sodium is mediated mainly through the adenosine triphosphate-dependent sodium-potassium pump, which is inhibited by cardiac glycosides such as ouabain (Figure 1). There exist in this cell, however, at least two other sodium transport systems that are not inhibited by ouabain (ouabain-insensitive pathways). These are the Na+, K+ cotransport system,[5] which catalyzes the coupled transmembrane efflux or influx of Na+ and K+ in the same direction, and the Na+, Li+ exchange or countertransport system, which represents a one-to-one exchange of Na+ for Na+ or Li+ for Na+ across the plasma membrane (Figure 1).[6] Detection of abnormalities in these transport systems in erythrocytes from patients who have essential hypertension is the main consideration in this review.

Garay and Meyer first noted abnormalities in the Na+, K+ cotransport system in erythrocytes from patients with essential hypertension.[7,8] This system is identified by examining Na+ and K+ efflux rates in the presence of ouabain and furosemide in erythrocytes preloaded with Na+ and depleted of K+.[7-9] Furosemide is the specific inhibitor of cotransport activity. Maximal outward furosemide-sensitive cotransport of Na+ and K+ is significantly reduced in erythrocytes from about 70% of patients with essential hypertension (Figure 2).[9] Moreover, a familial pattern of defective erythrocyte cotransport is seen in a substantial number of normotensive offspring from families with hypertension. Thus, it is possible that there is a genetic trans-

mission of this trait that would offer the potential of this assay to detect hypertension-prone offspring from families with a high prevalence of hypertension. Interestingly, patients with secondary hypertension (mostly renovascular hypertension) showed normal cotransport if they had no family history of hypertension, whereas those with a family history had reduced cotransport. The cotransport abnormality appears to occur independently of the level of blood pressure, duration of hypertension and sex and age of patients.[9] Garay and associates have proposed that decreased Na+ cotransport in hypertension is due to a reduced affinity of
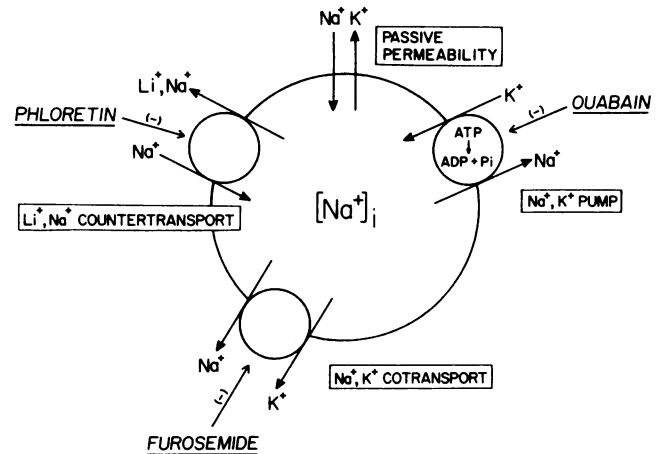

Figure 1.—Human erythrocyte sodium (Na+) transport systems that have been examined in hypertensive disorders. K+ = potassium, Li+ = lithium, ADP = adenosine diphosphate, ATP = adenosine triphosphate, Pi = inorganic phosphate.
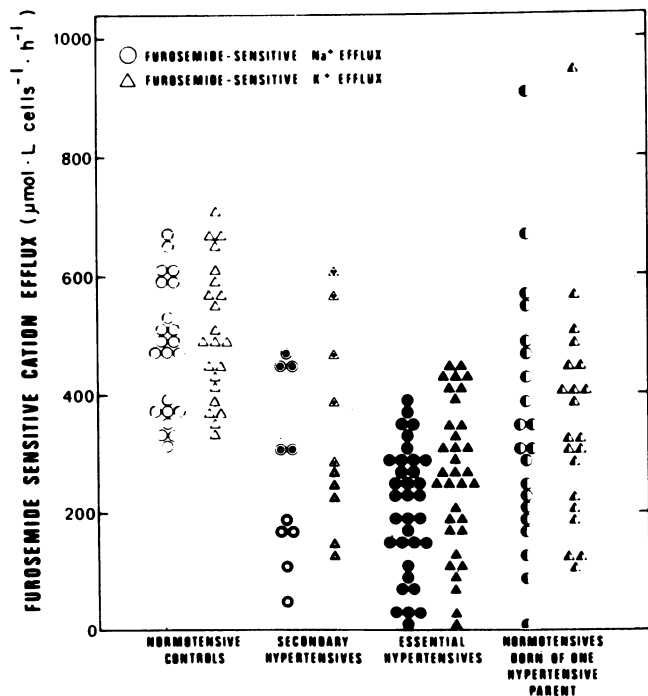

Figure 2.—Scatter diagram of the maximal rate of outward furosemide-sensitive sodium (Na+)-potassium (K+) cotransport in hypertensive disorders (from Dagher and Garay[9]).
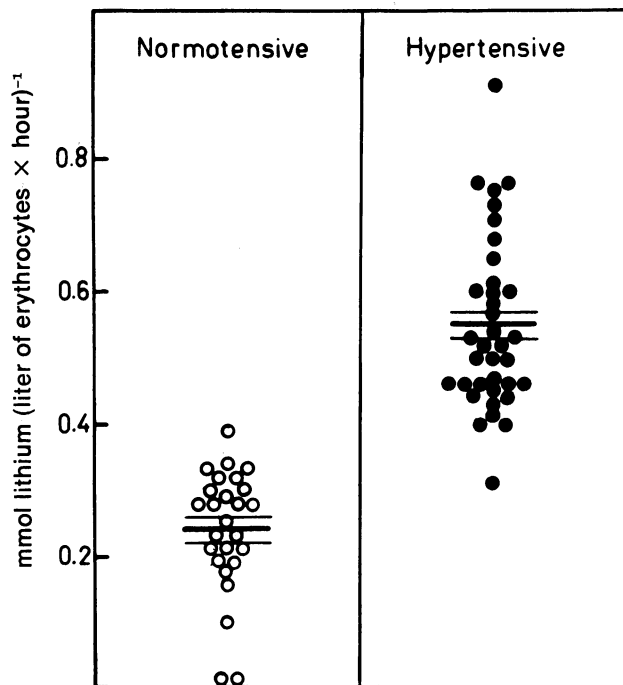
Figure 3.—Maximal rate of sodium-stimulated lithium efflux in erythrocytes of normotensive subjects and patients who have essential hypertension (from Canessa et al[18]).

internal Na^+ for the binding sites on the cotransport pathway.[10] Thus, in erythrocytes from essential hypertensive patients half-maximal cotransport stimulation occurs at an intracellular Na^+ concentration of about 20 mmol per liter of cells compared with 10 to 15 mmol in normotensive cells. At present it may be premature to comment on the possibility of the cotransport assay as a genetic marker of this disorder. Likewise, the pathogenetic significance of reduced cotransport remains speculative. One could postulate that in vascular smooth muscle cells a defective outward movement of Na^+ would lead to an abnormally high intracellular Na^+ concentration leading to excessive excitability of these cells.

Confirmation of reduced erythrocyte Na^+, K^+ cotransport in the essential hypertensive population has not been uniform. One report[11] noted reduced inward cotransport of rubidium, a substitute for potassium, in about 75% of patients who have essential hypertension, whereas others[12] detected this abnormality in less than half their patients. Normotensive offspring of hypertensive parents had intermediate cotransport values, but a great overlap was noted in individual values between normotensive and hypertensive groups. A study of erythrocyte cotransport from Cape Town, South Africa, included both black and white persons with essential hypertension.[13] This group noted that though mean cotransport values were lower in hypertensive persons, the overlap was too large to make it a useful genetic marker in hypertension. They also could find no significant difference in cotransport function between black and white persons who had hypertension. These findings contrast with another report

from the Ivory Coast of Africa where the incidence of hypertension is extremely high and levels of cotransport were uniformly low to absent in erythrocytes from hypertensive subjects.[14] Other studies have not been able to detect any abnormality in cotransport in patients with essential hypertension.[15-17] It is doubtful, however, that the latter reports using small study groups really disprove the original observation of abnormal outward Na^+, K^+ cotransport in some patients with essential hypertension, especially since the methods of measuring cotransport varied widely in these reports.

A second abnormality was reported by Canessa and co-workers[18] who found increased Na^+, Li^+ countertransport in erythrocytes from essential hypertensive subjects. This pathway is a one-to-one Na^+ exchange across the erythrocyte membrane and results in no net transport of ions. To measure countertransport, erythrocytes are loaded with lithium, which can substitute for internal sodium and has a greater affinity for the transport system, ensuring maximal rates of efflux. The difference in rate of loss of Li^+ from cells in the presence and absence of external Na^+ defines the Na^+, Li^+ countertransport pathway. Mean countertransport values were about twice as high in erythrocytes from persons who had essential hypertension with little overlap of values from those with normal blood pressure (Figure 3). Similar to the cotransport system, countertransport was also abnormally high in first-degree relatives of patients with essential hypertension. Previous studies on Li^+ transport in bipolar mood disorders also described a genetic transmission of the countertransport pathway.[19]

Several other studies have now confirmed that hypertensive subjects have increased erythrocyte Na^+, Li^+ countertransport.[12,20-23] Some of these reports found larger individual overlap and one study noted that only those patients with at least one hypertensive first-degree relative had elevated countertransport. Some have concluded that the assay is not a consistent marker for essential hypertension.[20] In a study of black school children a significant positive relationship between erythrocyte countertransport and systolic blood pressure was found,[21] thereby supporting a relationship between cellular sodium fluxes and blood pressure in this younger population. Normotensive offspring of hypertensive parents appear to have intermediate increases in erythrocyte countertransport. Woods and colleagues[22] examined the Na^+, Li^+ countertransport in 18 teenage sons of parents with essential hypertension and 21 sons of normotensive parents and noted that the rate was significantly increased in black and white male offspring of hypertensive parents. There may also be unexplained geographic differences in maximal rates of Na^+, Li^+ countertransport as there have been differences in absolute values reported from different parts of the world.[24] Only ongoing studies will further elucidate the genetic factors in countertransport function by examining large numbers of well-characterized families with essential hypertension. Two recent reports[17,25] using different assay techniques to measure Na^+, Li^+

exchange in erythrocytes could find little difference between hypertensive and normotensive persons.

Several questions about the importance of abnormal ouabain-insensitive Na^{+} transport pathways in essential hypertension remain to be answered. Does a hypertensive person who has abnormal erythrocyte sodium transport also have blood pressure sensitivity to a high sodium intake? This observation would offer the theoretic potential of using the erythrocyte assays as indicators of persons with blood pressure susceptibility to high salt diets. The exact relationship between a reduced erythrocyte Na^{+}, K^{+} cotransport system and a high Li^{+}, Na^{+} countertransport system in a hypertensive person also needs further explanation. Most investigators feel that they are two different transport systems, but it is also feasible that they may be two operationally different modes of the same transport system.[24] Uncertainty also exists as to whether genes determining transport activity of these two systems are identical or different. Studies are now in progress measuring both transport systems in the same hypertensive persons and their offspring. Preliminary findings indicate that there may be various subsets of erythrocyte Na^{+} transport abnormalities in the essential hypertensive population such as high countertransport-low cotransport, high countertransport-normal cotransport and perhaps other combinations.[26] Finally, the question remains whether the transport abnormalities in erythrocytes from persons with essential hypertension reflect the sodium and potassium ion transport capacity of more relevant target tissues such as vascular smooth muscle in essential hypertension. One postulate is that similar defects in vascular smooth muscle would result in high intracellular Na^{+} concentrations that could influence Ca^{++} concentrations, leading to activation of the contractile process and increased vascular resistance.[27]

Studies of the ouabain-sensitive sodium-potassium pump, the major system for cation transport in cells, show a spectrum of findings in hypertensive disorders. Many animal models of hypertension, especially those with volume-dependent hypertension, show reduced target tissue sodium-potassium pump activity whereas measurements of pump activity in tissues from persons with essential hypertension show varying results. There are several methods for characterizing the ouabain-sensitive sodium-potassium pump, including membrane sodium-potassium-adenosine triphosphatase activity, ^{86}Rb uptake, ouabain binding and measurement of unlabeled cation fluxes in the presence and absence of ouabain. These methods differ widely in techniques and tissue preparations.

Ouabain-sensitive Na^{+} transport (sodium-potassium pump) has been found to be reduced, normal or increased in cells from patients with essential hypertension. Edmondson and co-workers[28] reported reduced ouabain-sensitive sodium transport in leukocytes of patients who have essential hypertension. Other reports describe reduced ouabain-sensitive Na^{+} efflux rate constants in black Africans with essential hypertension[29] and in white patients.[30] Further investigations of racial differences in cation transport show that the ouabain-sensitive uptake of rubidium was lower in erythrocytes from black than from white normotensive persons.[31] Alterations in plasma volume and salt intake may also influence the activity of the sodium-potassium pump. Poston and colleagues[32] reported decreased ouabain-sensitive Na^{+} efflux rate constants in leukocytes from untreated persons with essential hypertension and further observed that diuretic therapy reversed this abnormality. Salt intake in hypertensive persons may also influence cellular Na^{+} transport, as one report indicated that a high salt intake in hypertensive persons reduced erythrocyte [22]Na efflux rate.[33]

Normal sodium-potassium pump activity in cells from patients who have essential hypertension and their normotensive offspring has also been observed.[12,34,35] One such study[34] could find no significant difference between erythrocytes of normotensive and essential hypertensive persons in sodium-potassium-adenosine triphosphatase activity and its Michaelis-Menten constant (K_m) value for adenosine triphosphate or in active ouabain-sensitive cation fluxes. They concluded that determination of these values in erythrocytes is not useful in the detection or diagnosis of essential hypertension. Ouabain-binding studies also show[35] no difference in the number of erythrocyte-binding sites between hypertensive and normotensive persons, suggesting normal sodium-potassium pump units in patients who have essential hypertension.

Actual increases in sodium-potassium pump activity have also been reported in cells from essential hypertensive patients. Woods and co-workers[31] showed that there was a greater activity of the sodium-potassium pump in fresh erythrocytes and Wambach and associates[36] reported greater adenosine triphosphatase activity in erythrocyte ghosts from patients with essential hypertension. Cation flux studies also show that outward ouabain-sensitive sodium efflux is increased in patients who have essential hypertension and certain of their normotensive offspring.[37] The increased sodium-potassium pump activity in essential hypertension has been proposed to be a compensatory response to abnormalities in the ouabain-insensitive transport systems described in the cells of these patients.

Considerable evidence supports the existence of a circulating humoral agent other than aldosterone that controls urinary sodium excretion by inhibiting sodium transport. This proposed natriuretic hormone probably acts on the sodium-potassium pump as it has been shown to inhibit renal sodium-potassium-adenosine triphosphatase activity.[38] Sodium-potassium-pump inhibition by natriuretic hormone in renal tissue may extend to other tissues such as vascular smooth muscle wherein the potential effects of sodium transport inhibition would lead to intracellular sodium accumulation. Thus, hypertensive persons, who are known to have an exaggerated natriuresis to sodium loading, may have exaggerated responses of a natriuretic-like hormone substance in response to salt loading, leading to a reduction of blood volume through enhanced renal sodium

excretion, while increasing inhibition of vascular smooth muscle pump activity. In volume-expanded animal models of hypertension there is a consistent reduction in pump activity as reflected by reduced arterial tissue rubidium uptake and cardiac microsomal adenosine triphosphatase activity that may be due to a circulating sodium transport inhibitor.[39,40] These observations have been extended by MacGregor and co-workers[41,42] to human essential hypertension in which they examined the ability of the plasma from hypertensive subjects to stimulate guinea pig renal glucose-6-phosphate dehydrogenase (G6PD), a marker of inhibition of the sodium-potassium pump. There was a significant increase in the ability of the plasma from patients with essential hypertension to stimulate G6PD compared with plasma from normotensive controls. These results suggest that patients with essential hypertension have enhanced levels of a circulating inhibitor of sodium-potassium pump activity. In cross-incubation experiments by adding leukocytes from normotensive persons to plasma from hypertensive patients there is impairment of sodium transport and this correlates inversely with the level of plasma renin in the hypertensive persons.[43] It was suggested that the degree of volume expansion and renin reduction related to the severity of pump suppression in these patients.

The idea of a putative circulating inhibitor of sodium transport in patients with essential hypertension is exciting and might explain some of the previously described sodium transport abnormalities in this disorder. The leading candidate for this inhibitory function seems to be a natriuretic hormone or a closely related compound. Isolation, purification and characterization of a sodium-potassium-pump inhibitor remains a problem despite several years of work in this area. Many experts agree it may be a peptide because enzymes that destroy peptides block its action. Another path of exploration has offered evidence that it may be a cardiac glycoside-like substance. Gruber and colleagues[44,45] showed in plasma from salt-loaded dogs a factor that cross-reacts with antidigoxin antibodies. They termed this digoxin-like substance "endoxin" and have identified it in animals that have hypertension.

Conceivably, from the abnormalities reported in membrane sodium transport and the proposed humoral control of this function, a stronger relationship between salt intake and hypertension may be established. Although certain observations continue to conflict, they point towards major research efforts in this area. Certainly the assays for membrane transport need to be improved as so little is known about the cotransport and countertransport systems and their contribution to cellular cation balance. At present these assays are difficult and complicated, making their clinical use somewhat limited. Any further progress in the role of natriuretic hormone in hypertension will depend partially on further isolation and identification of this substance. The relationship between these membrane and humoral defects in hypertension and the results of

epidemiologic and therapeutic studies of salt intake in hypertension are also beginning to be examined.

New Probes of the Renin-Angiotensin System

MICHAEL GOLUB, MD:* In 1898 Tigerstedt and Bergman noted that a kidney extract raised blood pressure in recipient rabbits.[46] They named the active material renin. Although this discovery did not excite the scientific world,[47] it provided the background for the important experiments of Harry Goldblatt in the 1930s. When Goldblatt found that renal ischemia could lead to hypertension in experimental animals,[48] the possibility that renin might underlie hypertension in humans became an important hypothesis.

The subsequent discovery of the renin-angiotensin-aldosterone cascade has led to a physiologic understanding of how this system can help raise blood pressure. Renin is a proteolytic enzyme that cleaves a decapeptide, angiotensin I, from a large substrate molecule manufactured in the liver. Angiotensin I is rapidly converted in the lung, kidney and plasma to the octapeptide, angiotensin II. The enzyme responsible for this important conversion reaction is called angiotensin-converting enzyme. Angiotensin II is a potent pressor substance but has the additional property of stimulating the adrenal gland to produce the sodium-retaining mineralocorticoid, aldosterone. Thus, any factor that stimulates renin release from the kidney would be expected to increase circulating levels of angiotensin II and aldosterone, both of which are potent hypertensive agents.

Clinical medicine has confirmed that in many patients who have disease of the renal arteries, renin-secreting tumors and other renal disorders (trauma, infarct, acute ureteral obstruction) hypertension can develop because of increased activity of the renin-angiotensin system. If renin activity can be lowered or angiotensin II can be antagonized in these patients, blood pressure will fall.

The role, however, of the renin-angiotensin system in maintaining elevated blood pressure in essential hypertension has continued to produce controversy. Brunner and Gavras have reviewed the physiologic role of the renin-angiotensin system in humans[49] and have concluded that this system developed to defend the organism from severe volume and sodium deficits. Thus, in normal persons living in high-sodium-intake societies the system should be relatively quiescent, but this may not be the case in hypertensive persons.

The findings of recent research have supported the concept that the renin-angiotensin system is very important in elevating blood pressure in a substantial proportion of patients who have essential hypertension.[50] It has been proposed that measurement of plasma renin activity as a function of urinary sodium excretion would allow categorization of hypertensive patients according to the degree that enhanced vasoconstriction or plasma volume expansion was contributing to the rise in blood pressure. In this proposed vasocon-

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striction-volume analysis,[50] patients with high renin activity have a vasoconstrictive hypertension because of excess activity of the pressor hormone angiotensin II and patients with low renin activity are hypertensive due to plasma volume expansion of uncertain cause. Patients with normal renin activity have elements of both volume expansion and vasoconstriction operating. Some investigators, however, have found this categorization of renin subgroups to be poorly reproducible in cases of essential hypertension.[51]

To probe the utility of such a scheme in predicting response to antihypertensive drugs, investigators have studied the blood pressure response in the renin subgroups to drugs that decrease volume or renin activity. The prediction that renin-lowering drugs such as propranolol hydrochloride would be most useful in subjects with high renin activity and that diuretics would be most efficacious in patients with low renin activity was validated by these studies.[52] It should be noted, however, that β-adrenergic-blocking drugs and diuretics have major antihypertensive properties unrelated to their effect on renin or volume. Thus, Woods and co-workers[53] found no difference in low-renin and normal-renin patients in their antihypertensive responses to the diuretic chlorthalidone compared with propranolol.

It became clear that to resolve this question more specific probes of the renin-angiotensin system were needed. Initially, analogues of angiotensin II were developed that exhibited the properties of competitive antagonists against the action of angiotensin II. The analogue saralasin acetate, which has been most extensively used in humans, is a peptide and must be administered intravenously. It is highly specific in its action. That is, it blocks blood pressure responses to infused angiotensin II but does not affect the response to other pressor agents such as norepinephrine.[54] Theoretically, then, this agent should block the effect of circulating angiotensin II and show the degree to which angiotensin participates in raising blood pressure. Indeed, patients with high renin activity, including many but not all patients who have renovascular hypertension, show a blood pressure fall when saralasin is administered.[54] Subjects with normal renin generally show little change in blood pressure.

Does this mean that hypertensive patients with normal renin activity do not have an angiotensin-dependent component to their blood pressure elevation? Not necessarily, for low-renin patients who have hypertension often have pressor rather than depressor responses to saralasin. This has been interpreted to mean that the analogue has intrinsic agonist or pressor properties.[55] When angiotensin receptors are not occupied, saralasin will cause a pressor response; when they are fully occupied by angiotensin (high renin states), the displacement by saralasin will lower blood pressure. But when the receptors are partially occupied (normal renin) both effects occur. The net result is that the use of saralasin tends to lead to an underestimation of the contribution of angiotensin to blood pressure maintenance. To compensate for this, saralasin is generally
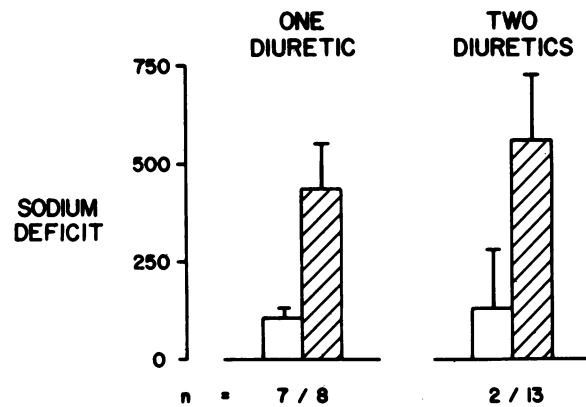

Figure 4.—Sodium deficit (in milliequivalents) achieved during diuretic administration in patients with essential hypertension undergoing saralasin administration. Hatched bars are saralasin responders; open bars are nonresponders. (Reprinted with permission from the American Heart Association and Thananopavarn et al.[56])

used following diuretic administration. Volume depletion tends to increase the relative contribution of angiotensin to blood pressure regulation. However, the precise degree of volume depletion necessary to offset the agonistic activity of saralasin is not known. We found that of 15 hypertensive men, none responded with a blood pressure drop when they did not take medications for four weeks but 8 had response after five days of diuretic therapy (metolazone, 5 mg daily) and 13 had response after spironolactone was added (400 mg daily) for five days.[56] Furthermore, the responders tended to have greater sodium losses to diuretic than the nonresponders (Figure 4). Thus, diuretic therapy, if given in sufficient amounts for long enough periods, will convert most hypertensive patients to saralasin responders. In addition, patients are heterogeneous in their natriuretic response to the same dose of diuretics. This makes it difficult to standardize the saralasin test as a direct measure of the degree of participation of angiotensin in essential hypertension.

The latest and perhaps most exciting advance in probing the renin-angiotensin system has been the development of converting-enzyme antagonists. These agents inhibit the activity of the enzyme that removes a dipeptide from angiotensin I to form angiotensin II. The initial compounds were isolated from the venom of a pit viper and a nonapeptide was synthesized. This material required intravenous administration, but subsequent and remarkable chemistry resulted in the development of an orally active drug, captopril.[57] Administration of this compound results in promptly reduced circulating angiotensin II and aldosterone levels.

Theoretically, the depressor response to this drug should correlate with the level and importance of angiotensin II in maintaining blood pressure. In hypertensive patients blood pressure initially falls, then rises and then falls again during continued captopril therapy.[58] Although the mechanism of this triphasic blood pressure response is unclear, it would appear that the initial and chronic depressor effects of captopril correlate well

with blood pressure dependency on the renin system. Thus, patients with high renin activity had the greatest fall, but subjects with normal renin also showed significant decreases. This provided further evidence that angiotensin II plays a role in normal-renin as well as high-renin hypertension.

Once again, things are not that simple, as it is now evident that captopril has multiple mechanisms of antihypertensive action. Many investigators have not found a close correlation between renin activity and blood pressure response to captopril.[59] Other hypotensive mechanisms for the action of converting-enzyme inhibitors must be considered. For years it has been known that this enzyme is also involved in the degradation of vasodilatory kinins so that inhibition of converting enzyme might increase kinin concentrations in the blood or in the kidney. In addition, there is evidence that vasodilatory prostaglandins may be stimulated by captopril. Moore and associates[60] showed that administration of inhibitors of prostaglandin synthesis blunts the hypotensive action of captopril. This mechanism may be particularly relevant to the hypotensive response seen in some low-renin patients.[61] Even normotensive subjects who have a normal sodium intake may show a significant fall in blood pressure with administration of captopril. Interestingly, this fall was completely blocked by indomethacin, a prostaglandin-synthesis inhibitor, but the fall seen after a low salt diet and the administration of captopril was not altered by indomethacin.[62]

It should be remembered that both angiotensin II and aldosterone levels are lowered by converting-enzyme inhibitors and both may play a role in blood pressure control. This is shown by some recent studies in hypertensive rat models. In spontaneously hypertensive rats, a significant fall in blood pressure follows inhibition of converting enzyme. This response is prevented by replacing adrenal steroids. In the one-clip, two-kidney hypertensive rat model, however, the hypotensive effect of captopril was not altered by steroid replacement.[63]

It is also conceivable that captopril has actions within the resistance vessels that are distinct from its effects on circulating angiotensin levels. Antonaccio and Kerwin[64] showed that captopril administration to spontaneously hypertensive rats decreased the vascular response to nerve stimulation. They hypothesized that in blood vessels local production of angiotensin may be important to the action of norepinephrine released by nerve stimulation. This local angiotensin formation could be decreased by captopril.

It would appear that converting-enzyme inhibition lowers blood pressure by mechanisms in addition to the decrease in angiotensin II levels. Although the ideal probe of the renin-angiotensin system may not have been found, the search has strengthened the position that this system is important in essential hypertension and has provided us with promising classes of therapeutic agents.

Heterogeneity of Renin-Angiotensin System

PETER EGGENA, PhD:* Although the renin-angiotensin system has been extensively studied,[65,66] many questions about its role in blood pressure homeostasis remain unanswered. Renin, an enzyme of renal origin, cleaves renin substrate, a protein of hepatic origin, to generate the decapeptide angiotensin I.[67,68] Angiotensin I-converting enzyme rapidly cleaves the decapeptide to produce the octapeptide angiotensin II.[69] This peptide hormone is known to contribute to blood pressure control via at least three pathways—direct vasoconstriction,[66,70] volume control via aldosterone[66,71] and by centrally mediated mechanisms.[72] Recent studies have indicated, however, a greater complexity of the system than originally assumed. Renin has been found to be heterogeneous with respect to enzyme activity and physical chemical properties[66,73-75] and several forms of renin substrate having different kinetic variables have been reported.[76-78] In this review I will address the recent discovery of inactive reninlike enzymes and the multiple forms of renin substrate (angiotensinogen) found in plasma of normotensive and hypertensive animals and in humans.

Renin

A significant additional increase in plasma renin activity is observed following preincubation of plasma with certain proteolytic enzymes,[79,80] exposure to acid pH[80,81] or storage at $-5°C$.[82,83] This additional reninlike activity has been termed inactive renin or prorenin. Not enough evidence is available to show that activated enzyme is a biosynthetic precursor of renin. Likewise, neither qualitative nor quantitative differences are seen in inactive renin patterns in normal and hypertensive persons.[84] The kidney may be a source of inactive renin[85] but in the anephric state other tissues can release inactive renin into the circulation.

Of major physiologic importance is whether inactive renin can be converted to the active form in the plasma of normal humans. Numerous in vivo studies have been done to acutely or chronically[86-89] stimulate or suppress active renin levels in plasma and measure resulting changes of inactive renin. Several investigators have reported reciprocal relationships between active and inactive renin,[86,90] whereas others have shown that the plasma level of inactive renin is not influenced by dynamic changes in active plasma renin.[88,91] Two recent studies have suggested that contrary to the hypothesis that inactive renin is a biosynthetic precursor of active renin, inactive renin may in part represent a partially degraded form of active renin, due to the natural process of renin catabolism.[92,93] Inactive renin appears to be heterogeneous and no significant differences are evident when comparing normal and hypertensive subjects, which argues against a role for this enzyme in the genesis of human hypertension. Because inactive renin is observed in anephric subjects and in arterial tissue, it is tempting to speculate that this enzyme may be a

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tissue enzyme similar to tonin,[94] capable of locally controlling vasoconstriction. Plasma levels of inactive renin may be a spillover product of the tissue enzyme system and therefore would not be responsive to dynamic alterations in plasma renin levels that originate from the kidney. In light of the seemingly contradictory findings, it is difficult to assess the physiologic control of inactive renin production or its role in blood pressure regulation.

Renin Substrate

Renin substrate, or angiotensinogen, essential for angiotensin generation, was originally thought to be present in plasma in such high concentrations that it could never be a rate-limiting factor for the generation of angiotensin. Recent kinetic studies have taken exception to this hypothesis. The Michaelis-Menten constant (K_m) of the renin reaction under normal physiologic conditions is about equal to the plasma concentration of renin substrate (Table 1). Therefore, under normal conditions the renin reaction proceeds at half the maximal rate. For the renin reaction to be independent of renin substrate concentration would require the renin substrate concentration-to-K_m to exceed 5. Table 1 shows that substrate to K_m ratio under several physiologic and pathologic conditions never exceeds 2.5. Renin substrate is therefore almost always rate limiting in the generation of angiotensin, but no statistically significant differences in renin substrate concentration have been found between normal and hypertensive subjects.

Renin substrate is heterogeneous in its molecular forms with respect to electrophoretic and immunologic properties. A high molecular weight form of renin substrate is found in women who have estrogenic hypertension, and the total renin substrate level may be elevated (Table 1). Similar findings were noted in the plasma of normal and hypertensive pregnant women at term (Table 1). Comparison of ethinyl estradiol with conjugated equine estrogens shows that ethinyl estradiol is more potent in stimulating the high molecular weight form of renin substrate.[95] This high molecular weight form has a higher affinity for renin than normal renin substrate, thus causing an accelerated rate of angiotensin I production in estrogenic hypertension. These studies suggest that in addition to measuring total renin substrate when assessing the plasma renin system of a person, one should also determine which forms of renin substrate are present.

The recent discovery of all of the components of the renin-angiotensin system in the central nervous system[72] and arterial tissue[84,96] suggest local generation of angiotensin II and possible control of blood pressure that is not evident from simply measuring plasma renin activity. This point of view is further strengthened by the recent observation that blood pressure can be lowered in hypertensive persons who have no apparent abnormality of the plasma renin system, by drugs that block the conversions of angiotensin I to angiotensin II.[97] All of the described studies show an unexpected complexity in the renin-angiotensin system, but also seem to clearly indicate that this system, when fully elucidated, may play a significantly more important role in blood pressure regulation than originally imagined.

Body Weight, Hormones and the Development of Hypertension

JAMES R. SOWERS, MD:* The relationship between obesity and hypertension has been recognized for decades. The association of excessive weight and high blood pressure probably has its inception in children and adolescents.[98,99] Yet the relationship between increasing age and hypertension also appears to be specific for affluent urban populations in whom there is increasing body weight with age.[100,101] Furthermore, reducing weight reduces blood pressure in both normo-

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TABLE 1.—Michaelis-Menten Constants (K_m) and Renin Substrate in Human Plasma

Physiologic and Pathologic Conditions	K_m ng AI per ml	Renin Substrate ng AI Eq per ml	High Molecular Weight Substrate Percent	Substrate to K_m Ratio
1 Healthy ♂ (n=13)	1,573±436	1,957±222	0.0	1.2
2 Essential hypertension (n=12)	1,551±575	1,459±235	0.0	1.0
3 Renovascular hypertension (n=6)	1,523±661	1,822±440	0.0	1.2
4 Hypertension associated with uremia (n=4)	1,354±360	2,595±610	0.0	1.9
5 ♀ on estrogen therapy, normotensive (n=20)	2,610±190*	5,150±1,530*	3.4	2.0
6 Estrogenic hypertension (n=5)	3,320±720*	6,800±2,450*	7.3	2.0
7 Term pregnancy plasma pool (n=2)	4,150	10,170	12.0	2.5

AI = angiotensin I

*Significantly elevated from 1 through 4.

tensive and hypertensive persons.[102-105] Several hemodynamic and hormonal mechanisms may explain why obesity leads to elevated blood pressure and how weight reduction lowers it. Increased total blood volume and cardiac output in the presence of normal peripheral vascular resistance are found in obese patients who have hypertension.[106] When these measurements are corrected for body surface area, however, investigators could not find differences between obese and nonobese hypertensive patients.[107] Salt restriction has also been suggested as a more important factor than caloric reduction in the lowered blood pressure associated with weight loss in obese patients.[108] However, recent studies have shown that weight loss is associated with reductions in blood pressure independent of salt intake (Figure 5).[103,104] Our group has observed that obese patients who have hypertension have higher supine plasma norepinephrine and epinephrine levels and greater norepinephrine responses to upright posture and isometric handgrip exercise than nonobese persons (Figure 6).[105] Plasma norepinephrine correlates with blood pressure levels in obese patients before weight loss and reductions in blood pressure are accompanied by reductions in plasma norepinephrine levels.[109]

Fasting and hypocaloric protein diets are associated with a natriuresis during the early days of caloric deprivation.[110-112] This natriuresis has been attributed to hyperketonemia,[110-111] relative hyperglucagonemia,[112] relative hypoinsulinemia[111-112] and mineralocorticosteroid resistance.[112] The natriuresis associated with hypocaloric diets could also result from alterations in catecholaminergic influences on electrolyte excretion in the kidneys. Circulating epinephrine and norepinephrine can cause reabsorption of sodium independent of changes in renal hemodynamics.[113,114] Dopamine also influences the regulation of renal sodium excretion, producing a natriuretic effect.[115-116] Our observations that during early caloric deprivation plasma dopamine level increases while epinephrine and norepinephrine levels decline[105,109] suggest that these alterations could affect renal catecholaminergic influences on electrolyte excretion and account for the natriuresis.

Weight and blood pressure reductions in obese patients on a hypocaloric diet are also associated with a fall in plasma renin activity and aldosterone levels.[104,105] There also appears to be a temporal relationship between the reduction in norepinephrine and the changes in renin activity during weight loss. Because the sym-

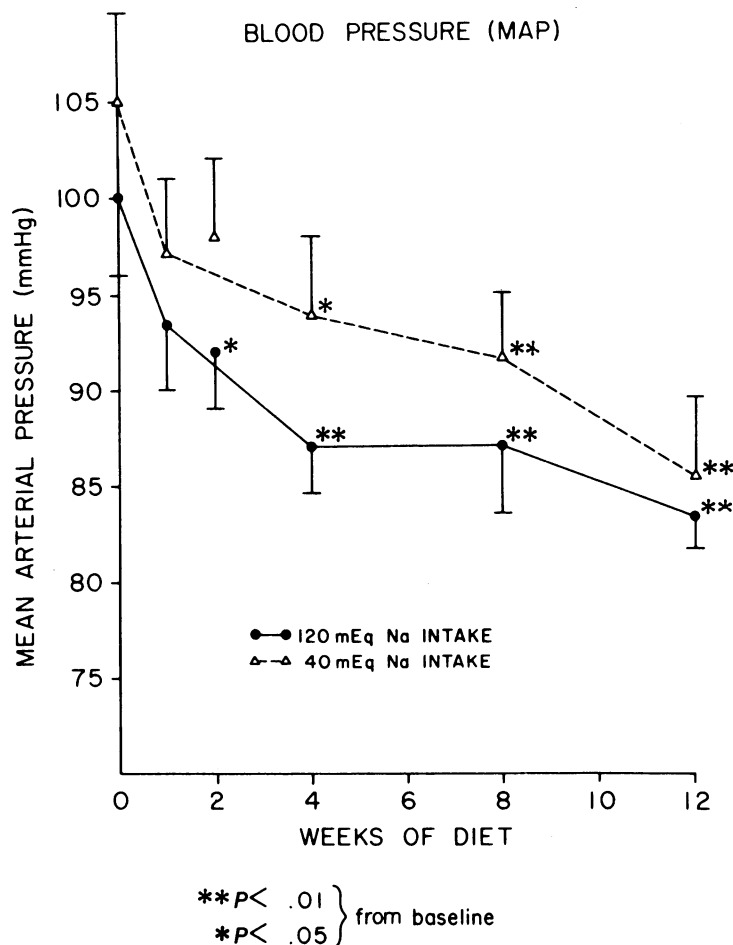BLOOD PRESSURE (MAP)

**P< .01 ⎫
*P< .05 ⎬ from baseline

Figure 5.—Reductions in mean arterial pressure during 12 weeks of extreme caloric restriction in obese patients on two sodium-intake regimens (from Tuck et al[104]). mmHg = millimeters of mercury, Na = sodium.

pathetic nervous system is an important factor modulating renin release, reductions in renin with caloric deprivation and weight loss could reflect diminished sympathetic nervous system activity. Thus, the sequence of events leading to depressor responses with caloric restriction in obese patients may result from initial effects on plasma catecholamines and secondary effects of reduced adrenergic activity on renal sodium excretion and the renin-angiotensin-aldosterone system.

A defect in the transmembrane sodium fluxes and a high intracellular sodium concentration have been reported in cells from experimentally hypertensive animals and in humans with hypertension as previously detailed. Obesity is also associated with increased erythrocyte intracellular sodium levels and reduced numbers of sodium-pump units as quantitated by ouabain binding and sodium-potassium-adenosine triphosphatase-mediated rubidium uptake.[117] A reduction in the level of sodium transport and higher intracellular sodium content have been described in liver and muscle from obese (ob/ob) mice.[118-120] We have recently examined the relationship between reduced sodium transport and blood pressure maintenance in obesity. Similar to other reports, there was reduced erythrocyte Na^+, K^+ ATPase

activity in obese patients compared with nonobese controls (Figure 7).[121] Cation transport, as measured by ^{86}Rb uptake by erythrocytes, was also reduced in parallel with the decrease in Na^+, K^+ ATPase activity. There was a negative correlation between pump activity and ^{86}Rb uptake versus the percentage of excess over ideal body weight. Although Na^+, K^+ ATPase activity and ^{86}Rb uptake by erythrocytes increased and intracellular sodium concentration decreased during 12 weeks of caloric restriction and weight loss, levels still remained abnormal compared with the nonobese controls (Figure 7). Importantly, however, there was no correlation of blood pressure with intracellular erythrocyte sodium levels or with the measurements of erythrocyte pump activity throughout the study. This negative relationship between erythrocyte pump activity and blood pressure in obesity would not support the concept that membrane transport abnormalities are the leading factor elevating blood pressure in obesity.

These observations offer evidence that several metabolic derangements associated with obesity contribute to the associated hypertension. These include increases in sympathetic nervous system activity, the renin-angiotensin system and certain aspects of disturbed
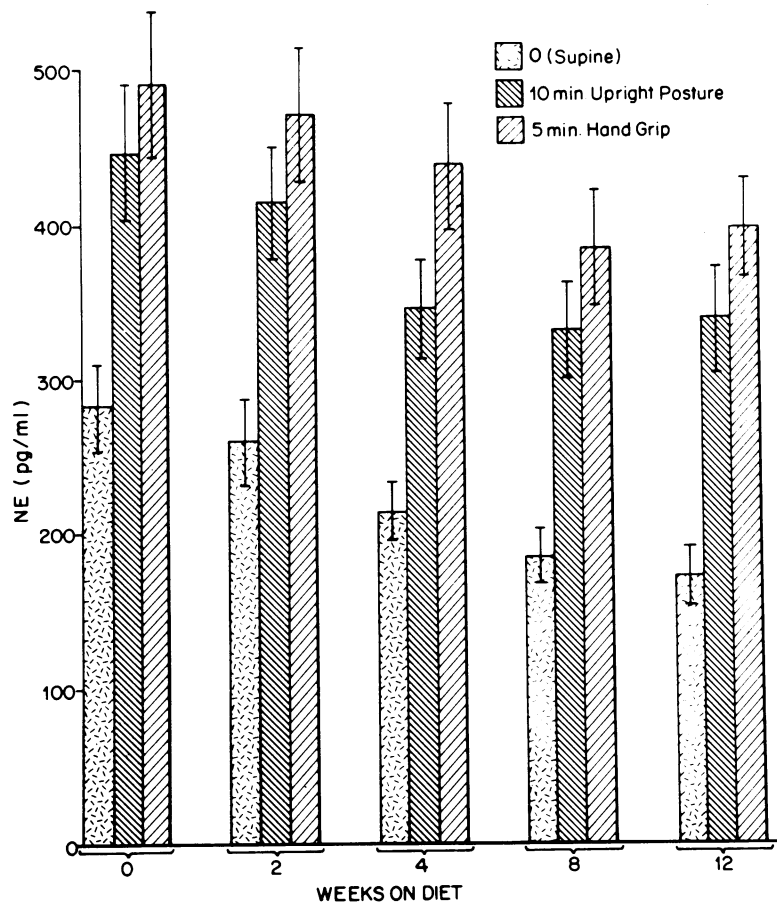

Figure 6.—Mean (±standard error of the mean) plasma norepinephrine (NE) responses to ten minutes of upright posture and five minutes of isometric handgrip exercise during weight reduction in obese patients on extreme caloric restriction (from Sowers et al[105]).

carbohydrate metabolism that may alter renal sodium excretion.

Newer Antihypertensive Drugs

MORTON H. MAXWELL, MD:* Several new antihypertensive drugs that directly attack the previously described hormonal systems in hypertensive persons have recently been approved for clinical use in the United States. These include the following: (1) atenolol (Tenormin), a β-adrenergic-blocking agent; (2) captopril (Capoten), a converting-enzyme inhibitor, and (3) calcium entry blockers, nifedipine (Procardia), verapamil (Calan, Isoptin) and diltiazem (Cardizem).

Atenolol

Atenolol has a unique profile in that it is relatively cardioselective and lipid-insoluble compared with other β-blockers.[122] A high binding affinity for the cardiac β_1-receptors should in theory result in fewer adverse side effects of β-blockers that are related to inhibition of peripheral β_2-receptors, such as asthma or cold extremities. Drugs that are lipid-insoluble have a longer plasma half-life and duration of action, permitting once-a-day dosage, and, because of their limited entry into the brain, may cause fewer central nervous system side effects such as sleep disturbances and abnormal dreams. Metoprolol tartrate (Lopressor) is also cardioselective but is lipophilic and has a shorter duration of action. Nadolol (Corgard) also has a long duration of action but is not cardioselective. All available β-blockers appear to have equal antihypertensive efficacy.[123] The flat dose-response curve and long duration of action of atenolol permit once-a-day dosing, and its relative cardioselectivity, especially in low doses, may benefit some patients. β-Blockers are widely used in Europe as step-one antihypertensive drugs. Because of their

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antiarrhythmic and cardioprotective properties, they will probably be used more frequently as monotherapy in the United States.

Captopril

Captopril inhibits the enzyme that converts angiotensin I to angiotensin II and inactivates bradykinin. Decreased circulating angiotensin II relieves arteriolar vasoconstriction and decreases aldosterone secretion, thereby lowering blood pressure and preventing sodium retention; increased bradykinin levels also tend to reduce blood pressure by other mechanisms.

The place of captopril in antihypertensive therapy is unclear. The occurrence of such side effects as taste disturbances and skin rash, as well as the more serious complications of membranous glomerulopathy and bone marrow suppression, may have been related to the large doses used (up to 500 mg per day). In mild to moderate hypertension, captopril is as effective as a diuretic or an adrenergic inhibitor, with very few adverse effects.[124] It is particularly effective in high renin forms of severe hypertension, such as renovascular hypertension or scleroderma.[125] Its antihypertensive effect is potentiated by diuretics and vasodilators. Black patients who have hypertension, perhaps because of lower renin levels, have been found to respond less well to captopril than white patients with hypertension.

In the package insert, it is stated that the use of captopril is restricted to patients with severe hypertension who have not responded to other antihypertensive drugs. With the use of smaller doses (12.5 to 25 mg twice a day), captopril will likely be useful as step-one therapy in moderate hypertension, with a diuretic added as step two if necessary.

Calcium Entry Blockers

Vascular smooth muscle contraction depends on intracellular calcium concentration. Several drugs of dif-
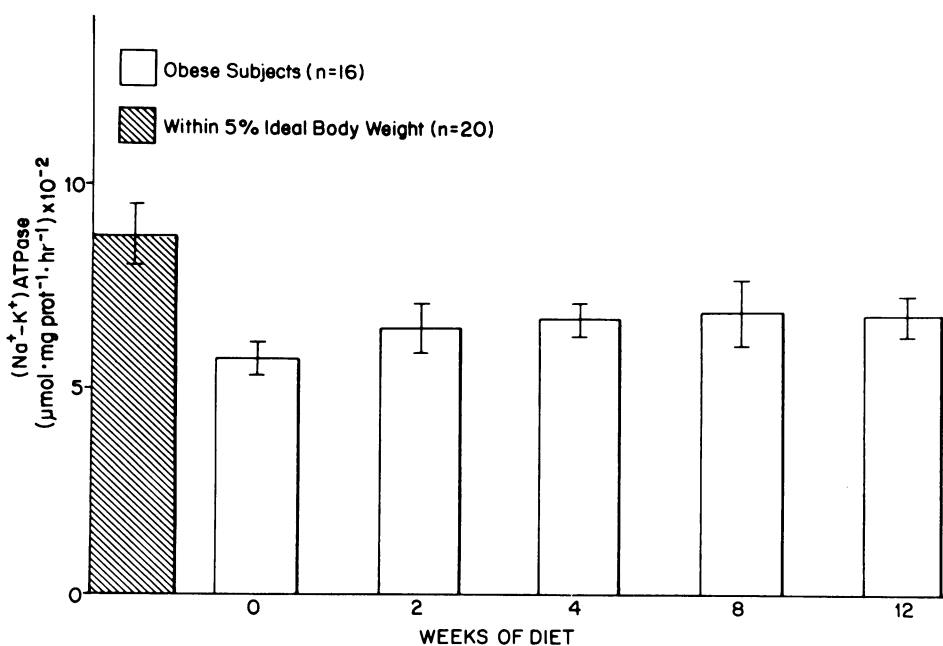

Figure 7.—Mean (±standard error of the mean) erythrocyte membrane sodium-potassium-adenosine triphosphatase (Na^+-K^+-ATPase) activity in nonobese subjects and in obese subjects during 12 weeks of weight reduction by extreme caloric restriction. (Data taken with the permission of *Clinical Science* and redrawn from Sowers et al[105]).

TABLE 2.—*Comparison of Calcium Entry Blockers*

Characteristics	Relative Effects		
	Nifedipine	Verapamil	Diltiazem
Circulatory			
Systemic resistance	↓↓↓↓	↓↓↓	↓↓
Heart rate	↑↑	N	N
Atrioventricular conduction ..	N	↑↑	↑
Cardiac output	↑↑	↑ or ↓	↑ or N
Side Effects			
Hypotension and facial flushing	+ + +	+ +	0
Headache and dizziness	+ +	+ +	+
Atrioventricular block	0	+ +	0
Heart failure	0	+	0
Constipation	0	+ +	0
Nausea and vomiting	+ +	+	0
Edema	+	0	0

↓ = slightly lowered, ↓↓ = moderately lowered, ↓↓↓ = greatly lowered, ↓↓↓↓ = very greatly lowered, ↑ = slightly raised, ↑↑ = moderately raised, N = no change, + = mild, + + = moderate, + + + = extreme, 0 = no effect.

fering pharmacologic configuration have the common property of inhibiting the slow calcium channel entry into arterial smooth muscle cells, thus reducing peripheral vasoconstriction and lowering blood pressure.[126] In keeping with the premise that increased intracellular calcium and sodium concentrations may have a primary pathogenic role in hypertension, the calcium entry blockers have little or no effect on the arterial pressure of persons with normal blood pressure.

The presently available calcium entry blockers have been extensively studied in ischemic heart disease and atrial arrhythmias and have thus far been approved by the Food and Drug Administration for use in only those conditions. Nevertheless, their use in the treatment of hypertension will likely become widespread before official approval.

It should be reiterated that the presently available calcium entry blockers do not share a common site of action or have similar configurations and thus have important clinical differences on cardiac performance, vascular contractility and side effects (Table 2). The common effects that these drugs have on the circulation include reduced arterial pressure, reduced heart rate (unless reflex tachycardia occurs) and decreased inotropic state of the myocardium that may be concealed by reflex changes in the heart rate, and reduced oxygen requirements of the heart. Like the β-blockers, they may prevent cardiac arrhythmias and myocardial reinfarctions, which would make them most appropriate in treating hypertensive patients who have coronary artery disease.

The following is the frequency of side effects reported in large series[126] of patients: 17% for nifedipine, the drug being discontinued in 5% because of intolerance; 9% for verapamil, with discontinuation in 1%, and 4% for diltiazem, with rare discontinuation. Thus diltiazem has the fewest side effects, but also is the least effective antihypertensive agent. Congestive heart failure and atrioventricular conduction defects are contraindications for verapamil, as is concomitant therapy with other myocardial depressants, such as β-blockers

and disopyramide. Nifedipine may be used safely in patients taking β-blockers and in patients with left ventricular dysfunction. In the near future, the most widely used calcium entry blocker for hypertension will likely be nifedipine.

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